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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Paper No. 33

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Appellant(s): David H. Gelfand et al

Mailed
10/19/94

Stacey R. Sias
For Appellant

Supplemental
EXAMINER'S ANSWER

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1803.

This supplemental examiner's answer is in response to the reply brief filed July 11, 1994(paper no. 32).

In response to the 112, first paragraph, rejection appellants make the following arguments.

Appellants urge in no. 1 beginning on page 1 that remarks in regard to the specification in support of the § 112, first paragraph, rejection are irrelevant and that changes in pH and presence or absence of nucleoside triphosphates is not analogous to the substitution of one non-ionic detergent for another. However, when the variations referred to in the specification are considerated in combination with the disclosure of Wu et al that Triton X-100 detergent will not stimulate bacterial DNA polymerase(paragraph bridging pages 21 and 22 of the examiner's answer), the combination becomes highly relevant.

In no. 2 beginning on page 3, appellants assert that the MBR product information sheet shows that one detergent will work. However, the one detergent disclosed by the sheet is Tween 20. This detergent is not used by Wu et al. The fact that Wu et al disclose that bacterial polymerase is not stimulated by Triton X-100 indicates unpredictability.

In no. 3 on page 4, appellants state that claim 62 was

addressed under the § 112 rejection in the answer on page 10 in regard to reaction buffer described on page 12 of the brief not containing a non-ionic detergent. However, it is again pointed out that the reaction mixture discribed on page 12 does not contain a non-ionic detergent. If the polymerase present contains the detergent this is not described on page 12. In any event, as pointed out on page 10 of the answer, the polymerase used in the reaction mixture of example XIV which appellants rely on to support claim 62 is that stored in the storage buffer disclosed on page 79, lines 10-14. Both the storage buffer and a buffer used for dilution contain the non-ionic detergents, NP-40 and Tween 20, gelatin and other ingredients as disclosed in example XIV on page 79 of the specification. In this example, NP-40 and Tween 20 are used together and Tween 20 is not used alone as in the MBR product information sheet. Additionally, this is not the same as using Triton X-100 alone when Wu et al found bacterial DNA polymerase not to be stimulated.

In no. 4 beginning on page 5, appellants urge that requiring additional experiments is without merit since no reference suggests that one non-ionic detergent in place of two has any different effect on stabilizing a purified thermostable DNA polymerase. However, the disclosure of Wu et al that bacterial DNA polymerase is not stimulated by Triton X-100 provides merit for requiring additional experiments. In addition to bacterial DNA polymerase, Wu et al also found that three known mammalian

cellular DNA polymerases were not stimulated(see abstract on page 789). Thus, a reason has clearly been provided as required by In re Chilowsky cited at the bottom of page 5 of the reply brief. The fact that certain buffer ingredients used in the examples are known in the prior art as buffer ingredients does not permit their omission when the working examples indicate that these buffer ingredients are needed to provide the stabilization desired.

Appellants refer to the 132 Declaration of the exhibit C attached to the brief as showing that gelatin is not needed. However, this is a 131 Declaration. In any event, since working embodiment(example XIV) requires gelatin, it appears that gelatin was determined to be needed after the experiments in the declaration were carried out. If gelatin was not important or had no affect, the working embodiment in the specification would not appear to require gelatin. When the present specification was filed, the presence of gelatin was apparently considered to be an improvement over gelatin not being present.

In no. 5 beginning on page 7, appellants urge that the differences in types of detergents are well known. However, while the structure and certain properties of detergents may be well known, it is not well known and predictable how different detergents will affect an enzyme and this is supported by Wu et al. Wu et al further supports that substituting one detergent for another can result in a non-workable invention. Wu wt al

support that if Triton X-100 is used as the non-ionic detergent in the claims the present invention will not work. Further support of the claims encompassing non-workable embodiments is that the working example in the specification requires a combination of two specific non-ionic detergents alone with other specific ingredients.

In no. 6 on page 8, appellants urge that the Akers 132 Declaration was submitted to traverse obviousness and the examiner has stated that this declaration is insufficient to provide enablement for the scope of the claims. However, the reason this declaration was commented on in regard to the 112 rejection was because appellants relied on this declaration in the brief in arguments traversing the 112 rejection. See the fourth paragraph on page 22 of the brief. Prior to the brief, appellants relied on this declaration only to traverse the 103 rejection. See page 17 of the amendment of 1/19/93(paper no. 24) and page 13 the preliminary amendment of 4/24/92(paper no. 20) where the declaration was previously relied on to traverse the 103 rejection.

In no. 7 on page 9, appellants urge that 131 and 132 Declarations have demonstrated that gelatin does not provide enhanced stability and that present commercial embodiments do not include gelatin. However, in the 132 Declaration filed of 4/24/94, in experiment 3 on page 6, when gelatin is present the detergents have been removed. There is no comparison of adding

gelatin to storage buffer #1 and comparing the result with the buffer containing the detergents without gelatin. Therefore, the declaration fails to establish that the same stability is obtained with or without gelatin when using storage buffer #1. Furthermore, even if gelatin can be omitted and obtain the desired result, storage buffer #1 still contains Tris, KCl, DTT, NP-40, Tween 20, EDTA, glycerol and has a pH of 8. The present invention as broadly claimed is clearly not commensurate in scope with storage buffer #1. In the 131 Declaration filed 1/19/93, item 11 on page 3 states that notebook page 101 describes a lot 2 enzyme storage buffer containing non-ionic detergent but not gelatin. However, the lot 2 buffer appears to be the same as storage buffer #1 used in experiments 2 and 3 of the 132 Declaration. The 131 Declaration like the 132 Declaration does not compare the storage buffer #1 not containing gelatin with the storage buffer containing gelatin. If gelatin has no affect and this was known before filing the application as appellants seem to be urging, then why is gelatin included as an ingredient in the working example of the specification? One would normally omit an ingredient that is not needed.

In response to the 103 rejection, appellants make the following arguments.

In no. 1 beginning on page 10, appellants urge in the last sentence on page 11 that reverse transcriptase and thermostable DNA polymerases are dissimilar, non-comparable and not predictive

of one another's properties and characteristics. However, while this may be the believe of some in the art. it is not universal. Feller et al describe(paragraph bridging cols 1 and 2) a reverse transcriptase as being a DNA polymerase having reverse transcriptase properties. While there are differences in the enzymes, both enzymes are polymerases and produce DNA. See Goff et al(col 1, lines 20-25) where it is disclosed that reverse transcriptase can use either RNA or DN templates for DNA synthesis. Further see Spiegelman at col 2, lines 21-26, where it is disclosed that the key properties of DNA polymerase are very similar to those of reverse transcriptases. These disclosures of prior art references indicate that contrary to appellants' arguments the enzymes can be considered analogous, and have similar properties. These comments also apply to arguments in no. 3 beginning on page 13.

In no. 2 on page 12, appellants urge that the Kaledin(1980) enzyme is a crude enzyme and is not the enzyme used in the experiments of the Akers' Declaration. However, Kaledin et al(1980) disclose on page 497(4th paragraph) isolation of the enzyme using affinity chromatography. As shown in Table 1 on page 495, the degree of purification is 140 and the isolated enzyme has a specific activity of 7658 units/mg protein. This isolated enzyme is not a crude enzyme. In the 132 Akers Declaration, there is no description of the purity of the Taq DNA polymerase used. The enzyme of Kaledin et al is clearly a Taq

DNA polymerase.

In no. 4 beginning on page 14, appellants urge that the Akers Declaration serves to refute the examiner's position that reverse transcriptase is predictive of bacterial thermostable polymerase. However, as noted above in the response to part 1, prior art references disclose that these two enzyme are similar. The result of a non-ionic detergent having no affect on the functionality of reverse transcriptase in experiment 1 of the declaration conflicts with the disclosure of Goff et al(col 8, lines 23-25 and col 20, lines 25-26) that a non-ionic detergent is needed to maintain reverse transcriptase activity. There is seen no reason to accept the declaration result as correct and the result of Goff et al as incorrect. As to the need for gelatin, why was gelatin required in the working example of the specification if it was known prior to filing the application that gelatin had no affect on activity? Even if gelatin is determined not to be required, the present specification and the declaration support only obtaining the desired stability with storage buffer #1 as used in experiments 2 and 3 of the 132 Declaration. The present claims clearly are not commensurate in scope with this storage buffer. These comments also apply to arguments in no. 5 beginning on page 15.

In response to no. 6, the DNA polymerase of Kaledin et al(1980) is capable of functioning without the presence of a non-ionic detergent. The present invention is not using the

detergent to make the enzyme function but to prevent the loss of activity on storage or make the DNA polymerase more stable. Moreover, it is unclear as to the intended meaning of "functionality" in the first line of page 4 of the 132 Declaration. Furthermore, in experiment 1 of this declaration, only NP-40 is used as the detergent. This is not consistent with the working example in the present specification and buffer #1 of experiments 2 and 3 of the declaration where both NP-40 and Tween 20 are used.

In response to arguments in no. 7, establishing a difference in amino acid sequence of the DNA polymerase and reverse transcriptase does not establish how the enzymes will differ in properties. As noted above, Spiegelman considers these two enzymes to be very similar in key properties.

It is granted as urged by appellants in no. 8 that Wu wt al use a template-primer. However, as stated on page 22 of the answer, Wu et al tested detergents individually and used Triton X-100 when bacterial DNA polymerase was not stimulated, and not a combination of specific detergents as in the working example of the specification and as in storage buffer #1 in experiments 2 and 3 of the 132 Declaration.

In response to no. 9 beginning on page 19, the finding by Wu et al that Triton X-100 will not stimulate bacterial DNA polymerase is clearly an indication of unpredictability. The working example in the present specification fails to establish

that Triton X-100 alone is operable as a non-ionic detergent in the claimed invention. As set forth above and in the previous examiner's answer, the working example in the specification and experiments in the declarations establish only that a combination of the non-ionic detergents, NP-40 and Tween 20, and other ingredients stabilize a thermostable nucleic acid polymerase as claimed.

For the above reasons and for reasons in the examiner's answer of May 16, 1994(paper no. 30), it is believed that the rejections should be sustained.

Respectfully submitted,

DAVID M. NAFF
PRIMARY EXAMINER
ART UNIT 1823

DMN
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Stacey R. Sias
Roche Molecular Systems, Inc.
1145 Atlantic Avenue
Alameda, CA 94501